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<p>(21) International Application Number: PCT/EP98/00190</p> <p>(22) International Filing Date: 14 January 1998 (14.01.98)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>A 61/97</td> <td>16 January 1997 (16.01.97)</td> <td>AT</td> </tr> <tr> <td>A 62/97</td> <td>16 January 1997 (16.01.97)</td> <td>AT</td> </tr> </table> <p>(71) Applicant (for all designated States except US): BIOCHEMIE GESELLSCHAFT MBH [AT/AT]; A-6250 Kundi (AT).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): LUDESCHER, Johannes [AT/AT]; Kleinsoell 101, A-6252 Breitenbach (AT). MILLER, Ludwig [AT/AT]; Dreiheiligenstrasse 33, A-6020 Innsbruck (AT). STURM, Hubert [AT/AT]; Leopoldstrasse 40, A-6020 Innsbruck (AT). VEIT, Werner [AT/AT]; Kaiserjaegerstrasse 27, A-6330 Kufstein (AT). DECRISTOFORO, Martin [AT/AT]; Karwendelstrasse 6, A-6112 Wattens (AT). WOLF, Siegfried [AT/AT]; Bruggerstrasse 4, A-6230 Brixlegg (AT).</p> <p>(74) Agents: WYMANN, Gérard et al.; Novartis AG, Patent- und Markenabteilung, Lichtstrasse 35, CH-4002 Basel (CH).</p>		A 61/97	16 January 1997 (16.01.97)	AT	A 62/97	16 January 1997 (16.01.97)	AT	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published</p> <p><i>With international search report.</i></p> <p><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
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A 62/97	16 January 1997 (16.01.97)	AT						
<p>(54) Title: PURIFICATION PROCESS</p> <p>(57) Abstract</p> <p>Crystalline 2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid-S-mercapto-benzo-thiazoly-lester in form of an N,N-dimethylacetamide solvate; a crystalline salt of a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid with an amine of formula N(R₁)(R₂)(R₃), wherein R₁, R₂, and R₃ have various meanings, a crystalline sulphuric acid addition salt of a 7-[2-(2-aminothiazol-4-yl)-2-carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid; and the use of these salts in the production of cefixime, e.g. in form of a trihydrate.</p>								

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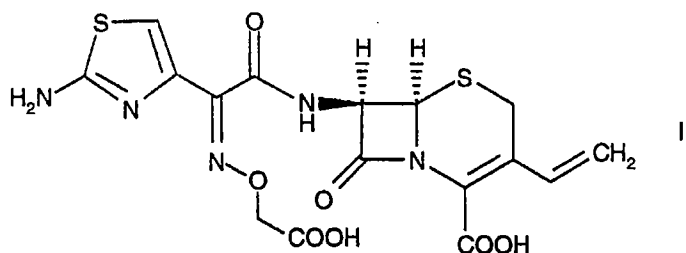
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Purification process

The present invention relates to a process for the purification of cefixime.

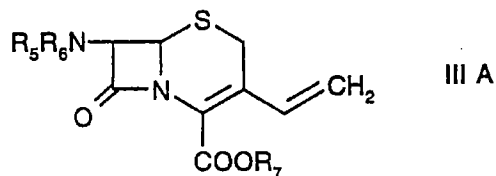
5 Cefixime of formula



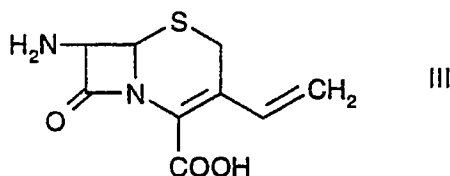
10 *e.g.* in form of a trihydrate, is a modern, orally available cephalosporin antibiotic having excellent antibacterial properties and high β -lactamase stability (see for example H.Yamanaka et al., J.Antibiotics (1985), 38(12), pp. 1738-1751).

According to prior art cefixime may *e.g.* be produced by reacting
a 7-amino-3-vinyl-3-cephem-4-carboxylic acid, *e.g.* of formula

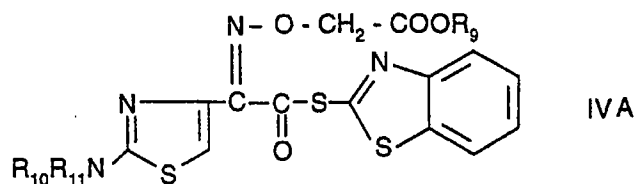
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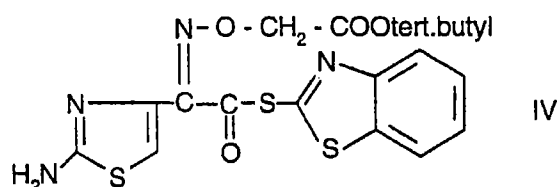
wherein R_5 and R_6 denote hydrogen or a leaving group and R_7 denotes hydrogen, alkyl, cycloalkyl, alkylaryl, aryl or arylalkyl; such as 7-amino-3-vinyl-3-cephem-4-carboxylic acid
20 of formula



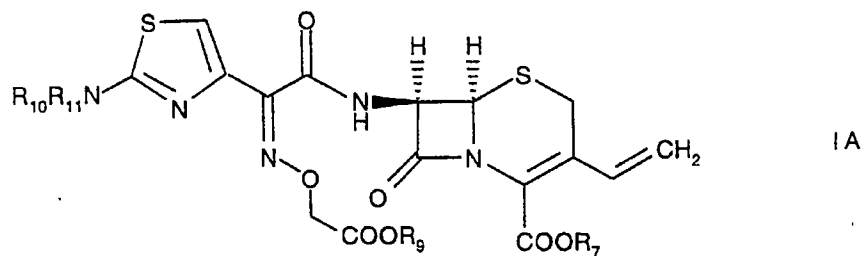
with a 2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetic acid of formula



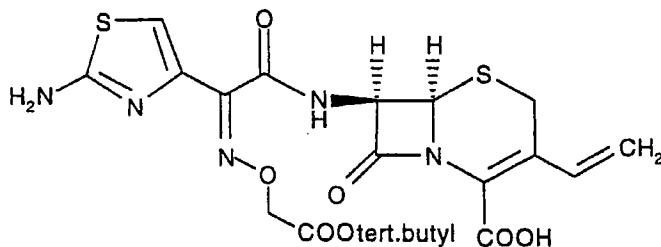
- wherein R_9 denotes alkyl, cycloalkyl, alkylaryl, aryl or arylalkyl and R_{10} and R_{11} denote
 5 hydrogen, silyl or acyl, *e.g.* in a reactive form, such as 2-(aminothiazol-4-yl)-2-(tert.butoxy-carbonylmethoxyimino)acetic acid-S-mercaptopbenzo-thiazoly-lester of formula



- 10 to give a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid, *e.g.* of formula



- 15 wherein R_7 , R_9 , R_{10} and R_{11} are as defined above, *e.g.* 7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula



and splitting off a group R₉, such as tert.butyl, and, if present, any R₇ and/or R₁₁, which is not hydrogen, to obtain cefixime of formula II, *e.g.* in form of a trihydrate.

Prior art processes may have disadvantages.

- 5 A compound of formula IA, *e.g.* of formula I, may be obtained in amorphous form. It was found that, due to its high solubility, solvents such as ethers having in general a low solubilizing effect are to be used for its isolation, *e.g.* according to EP 030 630 (see *e.g.* example 53) and thus undesired by-products which have to be separated off may be precipitated beside a compound of formula IA, *e.g.* of formula I. Isolation of a compound of
10 formula IA, *e.g.* of formula I in free acid form may also be effected from water but removal of water causes difficulties in a subsequent drying process.

- Removal of protecting groups of a compound of formula IA, *e.g.* of formula I under acidic conditions to obtain cefixime may cause difficulties, *e.g.* purification is to be carried out *via* chromatography as *e.g.* described in H.Yamanaka et al., J.Antibiotics (1985), 38(12), pp.
15 1738-1751) (yield of 34.1 %) and in AU 9526702 (WO 95/33753). According to EP 030 630, example 168, cefixime is precipitated after splitting off protecting groups by addition of diisopropylether having in general a low solubilizing effect and thus undesired by-products may additionally be precipitated.

- 20 According to the present invention surprisingly a new process for the production of cefixime in highly pure form has been found. The process according to the present invention may avoid disadvantages of prior art, *e.g.* by provision of intermediates, such as compounds of formulae I, II and optionally IV in crystalline form, which may have a high purification effect on the end product cefixime.

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In one aspect the present invention provides a process for the production of cefixime of formula II, comprising

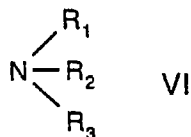
- a. reacting a 7-amino-3-vinyl-3-cephem-4-carboxylic acid of formula IIIA, wherein R₅ and R₆ denote hydrogen or a leaving group and R₇ denotes hydrogen, alkyl, cycloalkyl,
30 alkylaryl, aryl, arylalkyl or silyl, *e.g.* 7-amino-3-vinyl-3-cephem-4-carboxylic acid of formula III; *e.g.* in free form or in form of a salt,
with a 2-(aminothiazol-4-yl)-2-carboxymethoxy-imino)acetic acid of formula IVA, wherein R₉ denotes alkyl, cycloalkyl, alkylaryl, aryl or arylalkyl, R₁₀ denotes hydrogen and R₁₁ denotes hydrogen, silyl or acyl, *e.g.* 2-(aminothiazol-4-yl)-2-(tert.butoxycarbonyl-
35 methoxyimino)acetic acid-S-mercaptobenzo-thiazoly-lester of formula IV; *e.g.* in free

form or in form of a salt and/or in form of a solvate, *e.g.* an N,N-dimethylacetamide solvate;

to give a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula IA wherein R_7 , R_9 , R_{10} and R_{11} are as defined above, *e.g.* in free form or in form of a salt, *e.g.* 7-[2-(aminothiazol-4-yl)-2-

(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula I;
 b. reacting a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula IA, wherein R_7 , R_9 , R_{10} and R_{11} are as defined above, *e.g.* 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)-acetamido]-3-vinyl-3-

cephem-4-carboxylic acid of formula I, with an amine of formula

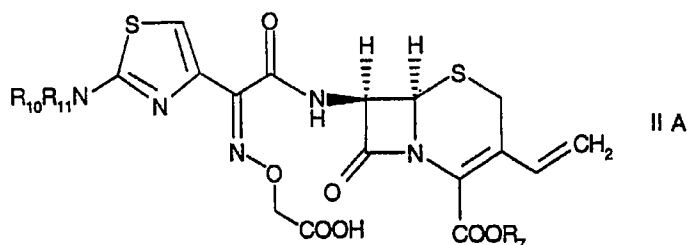


wherein R_1 , R_2 and R_3 independently of each other denote hydrogen, alkyl, cycloalkyl,

alkylaryl, aryl or aralkyl, to give a crystalline salt of a compound of formula IA, wherein R_7 , R_9 , R_{10} and R_{11} are as defined above, *e.g.* of formula I, with an amine of formula VI, wherein R_1 , R_2 and R_3 are as defined above,

c. reacting a compound of formula IA, wherein R_7 , R_9 , R_{10} and R_{11} are as defined above, *e.g.* in free form or in salt form, with sulphuric acid to obtain a 7-[2-(aminothiazol-4-yl)-2-

(carboxymethoxyimino)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid, *e.g.* of formula



wherein R_7 , R_{10} and R_{11} are as defined above, *e.g.* a 7-[2-(aminothiazol-4-yl)-2-

(carboxymethoxyimino)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula II, in form of a crystalline sulphuric acid addition salt, and, if desired,

d. converting a sulphuric acid addition salt of a compound of formula IIA, wherein R_9 , R_{10} and R_{11} are as defined above, *e.g.* a sulphuric acid addition salt of a compound of

formula II, into cefixime of formula II, *e.g.* in form of a solvate, such as a hydrate, *e.g.* trihydrate.

Any starting compound described herein may be produced as described herein, or
5 according to, *e.g.* analogous, known methods.

Step a. may be carried out as follows:

A 7-amino-3-vinyl-3-cephem-4-carboxylic acid, *e.g.* of formula IIIA, wherein R₅ and R₆ denote hydrogen or a leaving group, including *e.g.* a silyl group, *e.g.* R₅ denotes hydrogen and R₆ denotes hydrogen or a silyl group, preferably hydrogen; and R₇ denotes a group as
10 *e.g.* described for a corresponding group in *e.g.* H.Yamanaka et al., J.Antibiotics (1985), 38(12), pp. 1738-1751, AU 9526702 (WO 95/33753) and EP 030 630, the content of which is introduced herein by reference, and *e.g.* including hydrogen, alkyl, such as lower alkyl, *e.g.* tert.butyl, cycloalkyl, alkylaryl, *e.g.* (lower alkyl)aryl, arylalkyl, *e.g.* benzhydryl, or
15 silyl; such as hydrogen, alkyl or arylalkyl, preferably hydrogen; in free form or in form of a salt, *e.g.* an acid addition salt or, in case that R₇ denotes hydrogen, in form of a salt of the carboxylic acid group with a base, *e.g.* an amine salt; preferably in form of an amine salt; including *e.g.* a compound of formula III; may be reacted with
a 2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetic acid, *e.g.* of formula IVA, wherein
20 R₉, R₁₀ and R₁₁ denote a group as *e.g.* described for a corresponding group in *e.g.* H.Yamanaka et al., J.Antibiotics (1985), 38(12), pp. 1738-1751, AU 9526702 (WO 95/33753) and EP 030 630; the content of which is introduced herein by reference; and including in the meaning of R₉ alkyl, cycloalkyl, alkylaryl, aryl or arylalkyl, preferably alkyl, such as lower alkyl, *e.g.* butyl such as tert.butyl; and in the meaning of R₁₀ and R₁₁
25 hydrogen, silyl or acyl, *e.g.* R₁₀ denotes hydrogen and R₁₁ denotes hydrogen, silyl or acyl, *e.g.* formyl, alkanoyl, such as acetyl, or aralkanoyl, such as benzoyl, preferably formyl or hydrogen, *e.g.* hydrogen;
e.g. in form of an active derivative of a 2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)-acetic acid such as *e.g.* described in H.Yamanaka et al., J.Antibiotics (1985), 38(12), pp.
30 1738-1751, AU 9526702 (WO 95/33753), EP 030 630 and US 5,003,073, the content of which is introduced herein by reference; in free form, and in salt form and/or solvate form; preferably with 2-(aminothiazol-4-yl)-2-(tert.butoxy-carbonylmethoxyimino)acetic acid-S-mercaptopbenzo-thiazylester of formula IV, *e.g.* in solvate form, such as in form of an N,N-dimethylacetamide solvate.

It was found that an N,N-dimethylacetamide solvate of a compound of formula IV is particularly useful in a process of the present invention because it may be obtained in highly pure, *e.g.* crystalline form and it may be used as such, *e.g.* in a reaction, *e.g.* acylation, of a 3-vinyl-3-cephem-4-carboxylic acid. An N,N-dimethylacetamide solvate of a compound of formula IV may be obtained by dissolving 2-(aminothiazol-4-yl)-2-(tert.butoxycarbonyl-methoxyimino)acetic acid S-mercapto-benzthiazolyl ester in N,N-dimethylacetamide at appropriate temperature, *e.g.* around room temperature, such as at room temperature. An anti-solvent, such as a nitrile, *e.g.* acetonitrile, an ester, such as ethyl acetate, an ether, such as methyl-tert.butylether or water may be present in the reaction mixture. A compound of formula IV in form of an N,N-dimethylacetamide solvate may crystallize. The amount of N,N-dimethylsolvate is not critical. Conveniently per gram of a compound of formula I *e.g.* 0.5 ml to 4 ml, preferably 1 ml to 3 ml, such as 1.5 ml to 2.5 ml N,N-dimethylacetamide may be used. 2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid-S-mercapto-benzthiazoly ester may also be isolated directly from a reaction mixture for its production, obtainable *e.g.* from a reaction of 2-(aminothiazol-4-yl)-2-tert.butoxycarbonylmethoxyimino)acetic acid with benzthiazolyl disulfid and triphenylphosphine, in form of an, *e.g.* crystalline, N,N-dimethylacetamide solvate.

A crystalline compound of formula IV obtained may be isolated, *e.g.* filtrated off. A compound of formula IV in form of an N,N-dimethylacetamide solvate is new and forms also part of the present invention.

In another aspect the present invention provides a process as described above wherein a 2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetic acid is 2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid S-mercaptobenzo-thiazoly ester, *e.g.* of formula IV, *e.g.* in form of an N,N-diacetamide solvate; and 2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid S-mercaptobenzo-thiazoly ester, *e.g.* of formula IV, in form of an N,N-dimethylacetamide solvate.

A reaction of a 7-amino-3-vinyl-3-cephem-4-carboxylic acid with a 2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetic acid may be carried out as conventional, *e.g.* according to a, *e.g.* analogous, method, as *e.g.* described in H.Yamanaka et al., J.Antibiotics (1985), 38(12), pp. 1738-1751, AU 9526702 (WO 95/33753), EP 030 630 and US 5,003,073.

In a preferred embodiment of the present invention a 7-amino-3-vinyl-3-cephem-4-carboxylic acid, *e.g.* of formula III, *e.g.* in form of a salt, such as an amine salt, including *e.g.* a salt with a tertiary amine, such as triethylamine or tributylamine, an amidine such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or a

5 guanidine such as tetramethyl guanidine, preferably triethylamine; may be reacted in an organic solvent, including for example a halogenated hydrocarbon such as dichloromethane, an ester such as ethyl acetate or butyl acetate and a ketone, such as methyl isobutyl ketone, preferably an ester, such as ethyl acetate; and, if desired, in the presence of a co-solvent, such as an alcohol, for example ethanol or methanol,

10 water or an amide such as dimethylformamide, preferably water; or mixtures of individual solvents, *e.g.* as described above; with a 2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetic acid, for example in form of a reactive derivative, such as a 2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid-S-mercapto-benzothiazolyl ester, *e.g.* of formula IV, *e.g.* in form of an

15 N,N-dimethylacetamide solvate; at appropriate temperatures, *e.g.* below, about at, or above room temperature; such as from about 0°C to about 60°C, *e.g.* from 0°C to 60°C; such as from 10°C to 50°C, *e.g.* at room temperature.

A 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula IA, *e.g.* a compound of formula I, *e.g.* in form of a salt with an amine, *e.g.* a tertiary amine may be obtained.

20

For the isolation of a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid, *e.g.* of formula IA, such as of formula I, water may be added

25 to the reaction mixture, *e.g.* in the presence of a base, such as an amine, a bicarbonate or hydroxide, *e.g.* potassium, sodium. The phases formed may be separated. The aqueous phase may contain a compound of formula I, *e.g.* in form of a salt, *e.g.* with an amine, *e.g.* a tertiary amine. The aqueous mixture may be acidified, *e.g.* to obtain an pH of 1.5 to 3, *e.g.* 2 to 2.5, *e.g.* by addition of an acid, *e.g.* an inorganic acid, for example phosphoric acid; an organic solvent, *e.g.* a solvent as described above, preferably ethyl acetate, may

30 be added, if desired and the aqueous and the organic phase may be separated. The organic phase may contain a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid, *e.g.* of formula IA, *e.g.* a compound of formula I, in free form. Any R₇ and/or R₁₁ which is other than hydrogen, *e.g.* as described above, may

35 be split off as appropriate, *e.g.* as conventional, to obtain a 7-[2-(aminothiazol-4-yl)-2-

(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid wherein the amine group in the thiazolyl ring and/or the carboxylic group in position 4 may be free, *e.g.* a compound of formula I.

5 Step b. may be carried out as follows:

A 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid, *e.g.* of formula IA, wherein R₇, R₉, R₁₀ and R₁₁ are as defined above, in free form or in salt form, *e.g.* 7-[2-(aminothiazol-4-yl)-2-(butoxycarbonylmethoxyimino)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula I,

10 may be reacted with an an amine of formula VI, wherein R₁, R₂ and R₃ are as defined above, *e.g.* R₁, R₂ and R₃ independently of each other denote hydrogen, alkyl, cycloalkyl, aralkyl, aryl or alkylaryl, *e.g.* hydrogen, alkyl, cycloalkyl or aralkyl, such as hydrogen, alkyl or cycloalkyl. Preferably R₁, R₂ and R₃ each denotes cycloalkyl or alkyl, preferably alkyl, *e.g.* lower alkyl; such as ethyl; or R₁ and R₂ denote alkyl or cycloalkyl, preferably cycloalkyl
15 and R₃ denote hydrogen; or R₁ and R₂ denote hydrogen and R₃ denotes alkyl or cycloalkyl, preferably alkyl, such as (C₁₋₁₂)alkyl; using *e.g.* per equivalent of a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid about *e.g.* 1 to 3, preferably 1 to 2 equivalents of an amine of formula VI;
e.g. in the presence of an organic solvent including for example an ester, *e.g.* an acetic
20 acid ester, such as ethyl acetate or butyl acetate, a ketone, for example a dialkylketone, such as methyl isobutyl ketone and a chlorinated hydrocarbon, such as a chlorinated alkane, for example dichloromethane; if desired in the presence of a co-solvent, such as an alcohol, for example methanol, ethanol and isopropanol or water. An appropriate reaction temperature includes a temperature below, about at, or above room temperature;
25 such as from about 0°C up to the boiling point of a solvent used, *e.g.* under the reaction conditions, preferably, *e.g.* in case that dichloromethane is used as a solvent, about 0° to the boiling point of the solvent (mixture), including dichloromethane, used in the reaction mixture, such as about 10°C to 50°C.

30 If not otherwise defined herein alkyl includes (C₁₋₂₂)alkyl, *e.g.* (C₁₋₁₈)alkyl, such as (C₁₋₁₂)alkyl, *e.g.* (C₁₋₁₀)alkyl, *e.g.* (C₁₋₈)alkyl, such as (C₁₋₆)alkyl, *e.g.* (C₁₋₄)alkyl. Lower alkyl includes (C₁₋₆)alkyl, *e.g.* (C₁₋₅)alkyl, for example (C₁₋₄)alkyl. Cycloalkyl includes (C₃₋₈)cycloalkyl, such as (C₄₋₇)cycloalkyl, *e.g.* (C₅₋₆)cycloalkyl. Aryl includes (C₅₋₁₈)aryl, such as C₍₆₋₁₂₎aryl, preferably phenyl, naphthyl, *e.g.* phenyl. Silyl includes a silyl protecting group,
35 *e.g.* a conventional silyl protecting group, such as trialkylsilyl, for example trimethylsilyl. A

leaving group includes groups which may easily be split off, *e.g.* during an acylation reaction; including *e.g.* a silyl group. An acyl group includes (C₁₋₂₄)acyl, such as formyl, alkanoyl, aralkanoyl, aroyl and alkylaroyl, preferably formyl.

A crystalline salt of a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-
5 3-cephem-4-carboxylic acid, *e.g.* of formula IA, wherein R₇, R₉, R₁₀ and R₁₁ are as defined above, *e.g.* 7-[2-(aminothiazol-4-yl)-2-(butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula I, with an amine of formula VI, wherein R₁, R₂ and R₃ are as defined above, may be isolated from the reaction mixture, *e.g.* as appropriate, *e.g.* by filtration. Start and completion of crystallisation may be improved, *e.g.* by dilution of the
10 reaction mixture, *e.g.* with a solvent as described above, such as a solvent which was used for the reaction to obtain that amine salt; and/or, in case that a co-solvent, *e.g.* an alcohol was used, *e.g.* in reaction step b. by distilling off that co-solvent, if appropriate.

A crystalline salt of a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-
15 3-cephem-4-carboxylic acid, *e.g.* a compound of formula IA, wherein R₇, R₉, R₁₀ and R₁₁ are as defined above, such as of formula I, with an amine of formula VI, wherein R₁, R₂ and R₃ are as defined above, may improve the purity of the end product, *e.g.* cefixime, because it was found that it may be obtained in high purity. A crystalline salt of a compound of formula IA with an amine of formula VI is new and also forms part of the
20 present invention.

In another aspect the present invention provides a salt of a compound of formula IA, wherein R₇, R₉, R₁₀ and R₁₁ are as defined above, such as of formula I, with an amine of formula VI, wherein R₁, R₂ and R₃ are as defined above, *e.g.* triethylamine,
25 dicyclohexylamine or tert.octylamine; in crystalline form.

A crystalline salt of a 7-[2-(aminothiazol-4-yl)-2-(tert.butoxy-carbonylmethoxyimino)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid, *e.g.* of a compound of formula IA, such as of formula I, with an amine of formula VI may also be obtained directly from a reaction
30 mixture obtained in a reaction step a., *e.g.* in the presence of an amine of formula VI, without the isolation of a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid produced *e.g.* in a reaction step a..

A crystalline salt of a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-
35 3-cephem-4-carboxylic acid, *e.g.* of formula IA, wherein R₇, R₉, R₁₀ and R₁₁ are as defined

above, such as of formula I, with an amine of formula VI may be converted into a highly pure 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid wherein R_7 , R_9 , R_{10} and R_{11} are as defined above, such as of formula I, in free form; *e.g.* in the presence of an acidic agent, *e.g.* an inorganic or organic acid.

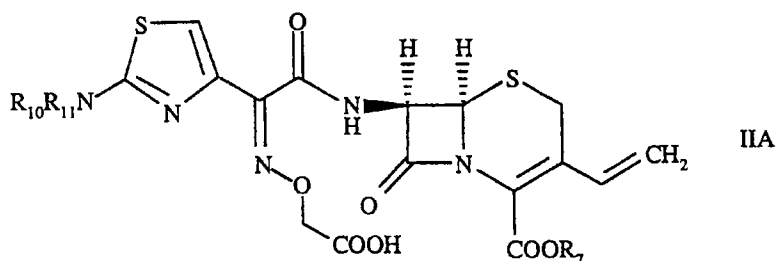
- 5 Any R_7 and/or R_{11} which is other than hydrogen, *e.g.* as described above, may be removed, *e.g.* as usual, to obtain a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid wherein the amine group in the thiazolyl ring and/or the carboxylic group in position 4 of the ring system may be free, *e.g.* to obtain a compound of formula I.

10

Step c. may be carried out as follows:

A 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid, *e.g.* of formula IA, wherein R_7 , R_9 , R_{10} and R_{11} are as defined above, such as of formula I, *e.g.* in free form or in salt form, such as in amine salt form, *e.g.* in form of a

- 15 salt with an amine of formula VI, *e.g.* as obtainable in reaction step b., may be converted into a compound of formula



- 20 wherein R_7 , R_{10} and R_{11} are as defined above, *e.g.* a compound of formula II, in free form, salt form and/or solvate, *e.g.* hydrate, such as monohydrate form, *e.g.* in crystalline form, by treatment with sulphuric acid;
e.g. in an organic, *e.g.* polar, solvent or solvent mixture, including *e.g.* a nitrile, such as acetonitrile; if desired in the presence of a co-solvent including water, a sulfoxide, *e.g.*
 25 dimethyl sulfoxide or sulfolane, or mixtures of individual solvents, *e.g.* as described above; *e.g.* in the presence of an acid, *e.g.* organic, such as formic acid, acetic acid.

The amount of sulphuric acid which may be used is not critical. In principle per equivalent of a compound of formula IA, *e.g.* of formula I, about 1 to 3, *e.g.* 1 to 2 equivalents may be used. If a compound of formula IA, *e.g.* of formula I, is used in form of a salt with a base,

- 30 such as an amine, *e.g.* an amine of formula VI, the amount of sulphuric acid may be

adapted, *e.g.* per equivalent amine an additional equivalent of sulphuric acid may be used. Conveniently per g of a 7-[2-(aminothiazol-4-yl)-2-(tert.carboxymethoxyimino)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula IVA, such as of formula IV, *e.g.* 0.2 ml to 0.6 ml, such as 0.3 to 0.4 ml of *e.g.* 95% sulphuric acid may be used.

- 5 The reaction temperature is not critical. The temperature may be below, about at, or above room temperature; such as from about 0°C to about 80°C, *e.g.* from 0°C to 80°C; such as from 10°C to 50°C, *e.g.* at room temperature. Higher temperatures may be used in case that R₇ and/or R₁₁ are not hydrogen and should be removed, to obtain a compound of formula II, *e.g.* simultaneously cleaving R₇ and/or R₁₁ and R₉ in, *e.g.* a compound of formula
10 IVA.

- Any R₇ and/or R₁₁ which is other than hydrogen, *e.g.* as described above, may be removed to obtain a compound of formula IIA, wherein the amine group in the thiazolyl ring and/or the carboxylic group in position 4 of the ring system may be free, *e.g.* a compound of
15 formula II, *e.g.* during sulphuric acid treatment, if appropriate in the presence of formic acid and/or acetic acid and/or water which may accelerate cleavage of *e.g.* protecting, groups; or by an appropriate *e.g.* conventional method.

- A compound of formula IIA, wherein R₇, R₁₀ and R₁₁ are as defined above, *e.g.* a
20 compound of formula II, in form of a crystalline sulphuric acid addition salt, *e.g.* in form of a hydrate, such as a monohydrate, may crystallise; addition of an anti-solvent to the reaction mixture, *e.g.* a nitrile, such as acetonitrile, may accelerate crystallisation.

- A sulphuric acid addition salt of cefixime of formula II may be obtained in form of a monohydrate, which may be de-hydrated, *e.g.* by drying. A sulphuric acid addition salt of
25 cefixime of formula II with a water content of less than 2%, *e.g.* 1.3% and less, may be obtained, *e.g.* by drying *in vacuo*. A dried sulphuric acid addition salt of cefixime of formula II, exposed *e.g.* to normal atmospheric moisture, may absorb atmospheric moisture and a sulphuric acid addition salt of cefixime of formula II may be obtained having a water content of about *e.g.* 3.4 to 3.6%, which is close to the theoretical water content of a
30 sulphuric acid addition salt of cefixime in form of a monohydrate, *i.e.* 3.16%.

- A crystalline salt of cefixime of formula IIA, such as of formula II, with sulphuric acid in form of a monohydrate may surprisingly be obtained in an easily isolatable form in reaction step c., surprisingly in high purity, *e.g.* improving the purity of cefixime obtainable in a process
35 according to the present invention. A crystalline salt of cefixime of formula IIA, *e.g.* of

cefixime of formula II, with sulphuric acid, *e.g.* in form of a monohydrate is new and also forms part of the present invention.

5 In another aspect the present invention provides a sulphuric acid addition salt, *e.g.* in form of a solvate, such as a hydrate, *e.g.* monohydrate of a compound of formula IIA, wherein R_7 , R_{10} and R_{11} are as defined above, *e.g.* of cefixime of formula II.

Step d. may be carried out as follows:

10 Conversion of a sulphuric acid addition salt of a compound of formula IIA, wherein R_9 , R_{10} and R_{11} are as defined above, *e.g.* a sulphuric acid addition salt of a compound of formula II, into cefixime of formula II, *e.g.* in form of a solvate, such as a hydrate, *e.g.* trihydrate may *e.g.* be carried out as conventional in a conversion reaction of an acid addition salt of a compound into a that compound in free form, *e.g.* in the presence of a base, *e.g.* ammonia, a carbonate, *e.g.* sodium, potassium; a bicarbonate, *e.g.* sodium or potassium;
15 a hydroxide; *e.g.* sodium or potassium, *e.g.* in solution, *e.g.* in water. A disodium, dipotassium or diammonium salt of a compound of formula IIA, *e.g.* cefixime of formula II, may be obtained. A compound of formula IIA, such as of formula II, may crystallise, *e.g.* in form of a solvate, *e.g.* a hydrate, such as a trihydrate, in the presence, *e.g.* by addition of an appropriate acid, *e.g.* as conventional, and, if desired in the presence of an organic
20 solvent such as a ketone, *e.g.* acetone or an alcohol, *e.g.* ethanol.

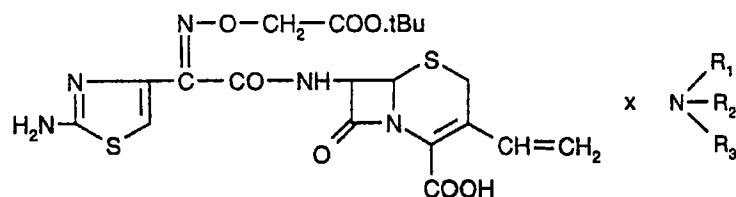
A compound of formula IIA, *e.g.* cefixime of formula II, *e.g.* in form of a trihydrate may be also obtained directly from a reaction mixture containing *e.g.* a compound of formula IIA, *e.g.* cefixime of formula II in form of a sulphuric acid addition salt, *e.g.* in form of a hydrate, *e.g.* by neutralizing the sulphuric acid present in the reaction mixture, *e.g.* by addition of an
25 appropriate base, *e.g.* as conventional.

From a compound of formula IIA, wherein R_7 , R_{10} and R_{11} are as described above, any R_7 , R_{10} and R_{11} which is other than hydrogen, may be removed to obtain a compound of formula IIA, wherein the amine group in the thiazolyl ring and/or the carboxylic group in
30 position 4 of the ring system may be free, *e.g.* a compound of formula II, *e.g.* according to an, *e.g.*, conventional method, either prior to conversion of a sulphuric acid addition salt of a compound of formula IIA, *e.g.* of formula II, into a compound of formula II in free form, *e.g.* in solvate form; or after such conversion.

2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid S-mercapto-benzo-thiazoly-lester in form of an N,N-dimethylacetamide solvate; and a crystalline salt of a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula IA, wherein R₇, R₉, R₁₀ and R₁₁ are as defined above, with an amine of
 5 formula VI, wherein R₁, R₂ and R₃ are as defined above; and a sulphuric acid addition salt of a compound of formula IIA wherein R₇, R₁₀ and R₁₁ are as defined in claim 1 are useful compounds in a process for the production of cefixime of formula II because each of these compounds may show a high purification effect and each of these compounds may contribute to the purity of the end product cefixime in a process according to the present
 10 invention. According to a process of the present invention cefixime may be obtained in excellent purity and a process according to the present invention is useful for the purification of, *e.g.* impure, cefixime.

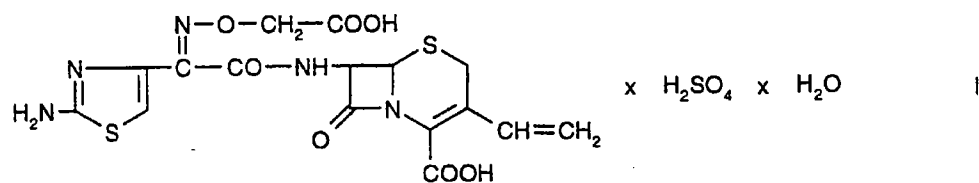
In another aspect the present invention provides the use
 15 of 2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid S-mercapto-benzo-thiazoly-lester in form of an N,N-dimethylacetamide solvate; and of a crystalline salt of a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula IA, wherein R₇, R₉, R₁₀ and R₁₁ are as defined in claim 1, with an amine of formula VI, wherein R₁, R₂ and R₃ are as defined in claim 1;
 20 and of a sulphuric acid addition salt of a compound of formula IIA wherein R₇, R₁₀ and R₁₁ are as defined in claim 1 in a process for the production of cefixime of formula II.

In another aspect the present invention provides crystalline salts of 7-[2-(aminothiazol-4-yl)-2-(tert.butoxy-carbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid
 25 of formula



30 wherein R₁, R₂ and R₃ either each signify an ethyl group, or R₁ and R₂ are cyclohexyl and R₃ is hydrogen, or R₁ and R₂ are hydrogen and R₃ is the tert.octyl group.

In another aspect the present invention provides a crystalline salt of cefixime of formula



5

In the following examples, which may illustrate the invention, but without limiting its scope, all temperatures are given in degrees Celsius.

Example 1**2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid-S-mercaptopbenzthiazolyester in form of a solvate with N,N-dimethylacetamide**

100 g of 2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid-S-mercaptopbenzthiazolyester (Purity 96.9 in % of HPLC area) are dissolved in 200 ml of N,N-dimethylacetamide. 2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid-S-mercaptopbenzthiazolyester in form of a solvate with N,N-dimethylacetamide crystallises, the precipitate is filtrated off, washed with acetonitrile and dried.

Crystalline 2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid-S-mercaptopbenzthiazolyester in form of a solvate with N,N-dimethylacetamide is obtained.

Yield: 75.3 g

HPLC purity: 99.2 in % of area

M.p. (decomp.): 115-125°

15

Example 2**7-[2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with tert.octylamine (2-amino-2,4,4-trimethylpentane)**

15 g of 7-amino-3-vinyl-3-cephem-4-carboxylic acid are suspended in 300 ml of ethyl acetate. 40 g of 2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid-S-mercaptopbenzthiazolyester in form of a solvate with N,N-dimethylacetamide in 30 ml of water are added to the reaction mixture. 8 g of triethylamine in 30 ml of ethyl acetate are added dropwise to the reaction mixture within ca. 1 hour. The reaction mixture is stirred for ca. 16 hours at room temperature and 300 ml of water are added. The phases formed are separated. To the aqueous phase 200 ml of ethyl acetate are added under stirring. The pH of the resulting mixture is adjusted to ca. 2.2 by addition of ca. 70 - 80 g of 75% phosphoric acid. The phases are separated and the aqueous phase is extracted with 200 ml of ethyl acetate.

To the combined ethyl acetate phases 12 g of tert.octylamine in 50 ml ethyl acetate are added within ca. 30 minutes under stirring. 7-[2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acet-amido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with tert.octylamine crystallises, the precipitate is filtrated off and dried.

Crystalline 7-[2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acet-amido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with tert.octylamine is obtained.

¹H NMR (MeOH-d₄): as in example 5 below.

5 Example 3

7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with triethylamine

10 g of 7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in 250 ml of ethyl acetate are treated with about 15 ml methanol
10 under stirring. A solution obtained is treated dropwise with 2.1 g of triethylamine in 20 ml of ethyl acetate within ca. 20 minutes. 7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with triethylamine crystallises, is filtrated off, washed with ethyl acetate and dried.
Crystalline 7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-
15 3-cephem-4-carboxylic acid in crystalline form of a salt with triethylamine is obtained.
M.p.: Decomposition from 200°

¹H NMR (MeOH-d₄): 7.08 (dd, J = 11.2 und 17.6 Hz, 1H); 6.92 (s, 1H); 5.84 (d, 1H); 5.45 (d, 1H); 5.22 (d, 1H); 5.17 (d, 1H); 4.66 (s, 2H); 3.73 and 3.59 (AB, d, J = 17.5 Hz, 1H);
20 3.19 (q, 2H); 1.48 (s, 9H); 1.30 (t, 3H).

Example 4

7-[2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with dicyclohexylamine

25 5.1 g of 7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid are dissolved in 50 ml of ethyl acetate, 5 ml of ethanol and 0.25 ml of water at 35°. 2 ml of dicyclohexylamine are added whilst stirring and the reaction mixture is seeded. 7-[2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with dicyclohexylamine crystallises, the precipitate is filtrated off, washed with ethyl acetate and dried.
30 Crystalline 7-[2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with dicyclohexylamine is obtained.
¹H NMR (MeOH-d₄): 7.02 (dd, J = 11.2 and 17.7 Hz, 1H); 6.92 (s, 1H); 5.79 (d, 1H); 5.31 (d, 1H); 5.12 (d, 1H); 5.10 (d, 1H); 4.65 (s, 2H); 3.65 and 3.54 (AB, d, J = 17.3 Hz, 1H);
35 3.21 - 3.14 (m, 2H); 2.05 (m, 4H); 1.8 (m, 4H); 1.6 (m, 2H); 1.48 (s, 9H); 1.2 - 1.4 (m, 10H).

Example 5**7-[2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with tert.octylamine**

- 5.1 g of 7-[2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid are dissolved in 50 ml of ethyl acetate, 10 ml of ethanol and 1 ml of water. The solution obtained is heated to 35° and seeded. 1.7 ml of tert.octylamine are added whilst stirring. 7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with tert.octylamine crystallises, is filtrated off, washed with ethyl acetate and dried.
- 10 Crystalline 7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with tert.octylamine is obtained.

- ¹H NMR (MeOH-d₄): 7.02 (dd, J = 11.2 and 17.7 Hz, 1H); 6.92 (s, 1H); 5.79 (d, 1H); 5.32 (d, 1H); 5.13 (d, 1H); 5.11 (d, 1H); 4.65 (s, 2H); 3.66 and 3.55 (AB, d, J = 17.3 Hz, 1H); 1.66 (s, 2H); 1.49 (s, 9H); 1.43 (s, 6H); 1.06 (s, 9H).

Example 6**7-[2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with tert.octylamine (directly from**

- 20 **acylation reaction mixture)**

- 20 g of 7-Amino-3-vinyl-3-cephem-4-carboxylic acid are suspended at room temperature in 200 ml of dichloromethane. 45 g of 2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid-S-mercaptobenzothiazolyl-ester, 4 ml of water and 10 g of triethyl-amine are added to the reaction mixture and the mixture is heated to ca. 30° to 35° under reflux.
- 25 An almost clear solution is obtained within ca. 3.5 hours. 5 ml of methanol are added and the mixture is filtered. The filtrate is heated to ca. 35° and a solution of 22 g of tert.octylamine in 100 ml of dichloromethane is added. Crystallisation starts *e.g.* after seeding. Ca. 100 ml of solvent are distilled off and ca. 200 ml of dichloromethane are simultaneously added. The suspension obtained is cooled to -10°. Crystalline 7-[2-
- 30 (aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with tert.octylamine precipitates, is filtrated off, washed with cooled (-20°) dichloromethane, and dried.
- Crystalline 7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with tert.octylamine is obtained.

M.p.: 190° (decomp.)

Content of by-products: 0.23%

Content of free cefixime: 0.03%

¹H NMR (MeOH-d₄): As described in Example 5.

5

Example 7

7-[2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with triethylamine (directly from acylation reaction mixture)

- 10 10 g of 7-Amino-3-vinyl-3-cephem-4-carboxylic acid are suspended in 100 ml of dichloromethane and the suspension obtained is cooled to 0°. 10 ml of water are added and 10 g of triethylamine are added dropwise to the reaction mixture. The temperature of the reaction mixture is adjusted to ca. 20° and 22 g of 2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid-S-mercaptobenzothiazolyl-ester are added.
- 15 The reaction mixture is stirred further for 3 hours at room temperature. 7-[2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with triethylamine precipitates, is filtrated off, stirred in 100 ml of dichloromethane, filtrated off and dried.
- Crystalline 7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-
- 20 3-cephem-4-carboxylic acid in form of a salt with triethylamine is obtained.

¹H NMR (MeOH-d₄): As described in Example 3.

Reference example

- 25 **7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid**
- 0.982 kg of triethylamine and 2.56 kg of 2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid-S-mercaptobenzothiazolyl-ester are added to a mixture of 1.044 kg of 7-amino-3-vinyl-cephem-4-carboxylic acid, 25.4 l of ethyl acetate, 0.94 l of
- 30 water and 2.4 l of methanol, cooled to 10°, under stirring. The reaction mixture obtained is cooled to 2° and stirred for 20 hours. A clear solution is obtained, which is mixed with 23.4 l of water and stirred for 20 minutes. The reaction mixture is heated to 20°. 3.5 N Hydrochloric acid is added and a pH between ca. 2.0 and 2.3 is adjusted. The phases formed are separated and the aqueous phase is extracted with ethyl acetate. 0.234 kg of
- 35 activated carbon are added to the combined ethyl acetate phases under stirring and

activated carbon is filtrated off. 23.4 l of water are added to the filtrate and the pH is adjusted to 8.0 by addition of ca. 0.93 l of 5 N sodium hydroxide solution. The phases are separated and the organic phase is extracted with water. Ethyl acetate traces in the mixture are removed by evaporation. The aqueous phase is mixed with 0.053 kg of
5 activated carbon under stirring and activated carbon is filtrated off. 6 N Hydrochloric acid is added to the reaction mixture and a pH of about 2.3 is adjusted. The suspension is cooled to 5° and stirred for 30 minutes at that temperature. 7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid precipitates, is isolated by centrifugation, washed with water and dried.
10 7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in solid form is obtained.

HPLC content: 85.9 %; H₂O: 4.3 %; Free cefixime: 1.6 %

Purity in % of HPLC area: 92.84 %

15

Example 8

Sulphuric acid addition salt of 7-[2-(2-aminothiazol-4-yl)-2-carboxymethoxyimino]acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a monohydrate

To a mixture of 40 g of 7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)-
20 acetamido]-3-vinyl-3-cephem-4-carboxylic acid, 40 ml of formic acid and 400 ml of acetonitrile, 12 ml of 95% H₂SO₄ are added at room temperature. A sulphuric acid addition salt of 7-[2-(2-aminothiazol-4-yl)-2-carboxymethoxyimino]acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a monohydrate crystallizes, is filtrated off, washed with acetonitrile and dried.
25 A crystalline sulphuric acid addition salt of 7-[2-(2-aminothiazol-4-yl)-2-carboxymethoxyimino]acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a monohydrate is obtained.

Cefixime content: 76.3% (HPLC)

H₂SO₄ content: 19.0% (ion chromatography)

30 Acetonitrile content: 0.84% (GC)

Water content: 1.3% (KF)

A part of 7-[2-(2-aminothiazol-4-yl)-2-carboxymethoxyimino]acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a monohydrate, obtained after drying is equilibrated in air over
35 night. Water content: 3.4% (KF)

Example 9**Sulphuric acid addition salt of 7-[2-(2-aminothiazol-4-yl)-2-carboxymethoxyimino]acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a monohydrate**

To a solution of 20 g of 7-[2-(2-aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a salt with tert.octylamine, 20 ml of formic acid and 200 ml of acetonitrile. 8 ml of 95% H₂SO₄ are added dropwise within 5 minutes and the mixture is seeded and stirred at room temperature and in an ice bath. A sulphuric acid addition salt of 7-[2-(2-aminothiazol-4-yl)-2-carboxymethoxyimino]-acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a monohydrate crystallizes, is filtrated off, washed with acetonitrile and dried.

A crystalline sulphuric acid addition salt of 7-[2-(2-aminothiazol-4-yl)-2-carboxymethoxyimino]-acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a monohydrate is obtained.

Purity (HPLC): 99 % (in % of HPLC area)
Cefixime content: 75.7% (HPLC)
H₂SO₄ content: 18.6% (ion chromatography)
Acetonitrile content: 1.8% (GC)
Water content: 1.9% (KF)

20

Example 10**Cefixime production from a sulphuric acid addition salt in form of a monohydrate**

14.87 g of a sulphuric acid addition salt of 7-[2-(2-aminothiazol-4-yl)-2-carboxymethoxyimino]acetamido]-3-vinyl-3-cephem-4-carboxylic acid in form of a monohydrate are suspended in 148 ml of water and diluted ammonia is added to adjust a pH of 6.0. 2.97 g of activated carbon are added, the reaction mixture is stirred at room temperature and activated carbon is filtered off. The filtrate is diluted with water to give a total volume of about 600 ml, mixed with 300 ml of ethanol and heated to 28°. The pH is adjusted to ca. 3.5 by addition of 6 N HCl. Seeding crystals are added. Cefixime in form of a trihydrate crystallizes. The resultant suspension is stirred for one hour at 28°, the pH is adjusted to ca. 2.5 and the suspension is stirred at room temperature and in an ice bath. Crystalline cefixime in form of a trihydrate is filtrated off, washed with water and dried.

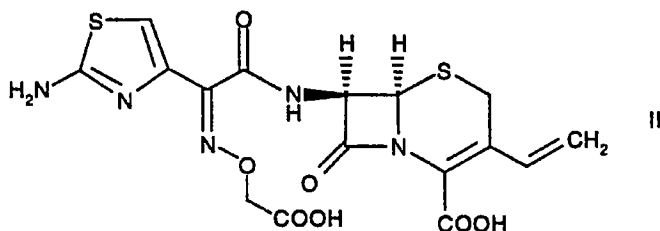
Crystalline cefixime in form of a trihydrate is obtained.

Purity (HPLC): 99.4 in % of HPLC area.

35

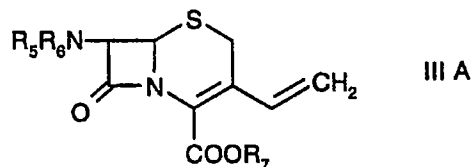
Patent Claims

1. A process for the production of cefixime of formula

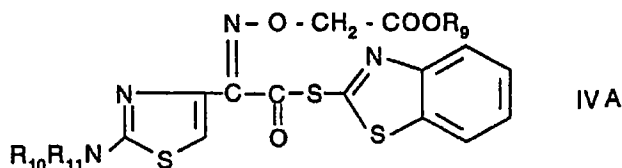


comprising

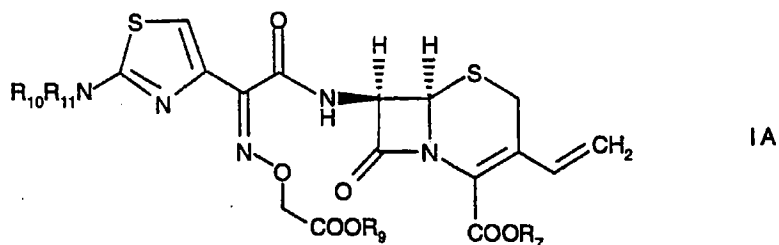
a. reacting a 7-amino-3-vinyl-3-cephem-4-carboxylic acid of formula



wherein R_5 and R_6 denote hydrogen or a leaving group and R_7 denotes hydrogen, alkyl, cycloalkyl, alkylaryl, aryl, arylalkyl or silyl; with a 2-(aminothiazol-4-yl)-2-carboxymethoxyimino)acetic acid of formula



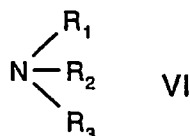
wherein R_9 denotes alkyl, cycloalkyl, alkylaryl, aryl or arylalkyl, R_{10} denotes hydrogen and R_{11} denotes hydrogen, silyl or acyl, to give a 7-[2-(aminothiazol-4-yl)-2-(carboxy-methoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula



wherein R_7 , R_9 , R_{10} and R_{11} are as defined above,

- b. reacting a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula IA, wherein R_7 , R_9 , R_{10} and R_{11} are as defined above

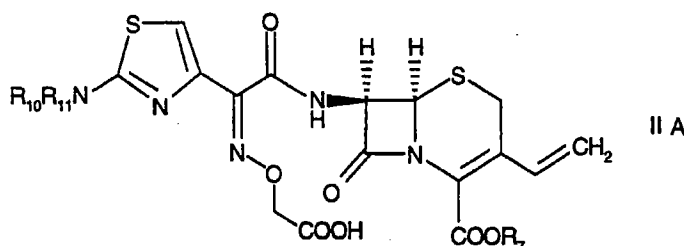
5 with an amine of formula



wherein R_1 , R_2 and R_3 independently of each other denote hydrogen, alkyl, cycloalkyl, alkylaryl, aryl or aralkyl,

10 to give a crystalline salt of a compound of formula IA, wherein R_7 , R_9 , R_{10} and R_{11} are as defined above with an amine of formula VI, wherein R_1 , R_2 and R_3 are as defined above,

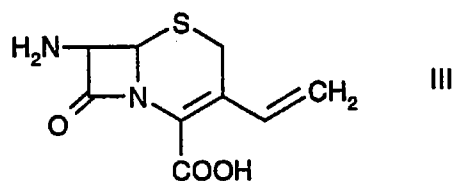
- c. reacting a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula IA, wherein R_7 , R_9 , R_{10} and R_{11} are as defined above, with sulphuric acid to obtain a compound of formula



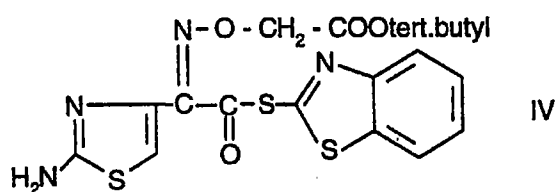
20 wherein R_7 , R_{10} and R_{11} are as defined above, in form of a crystalline sulphuric acid addition salt, and, if desired,

- d. converting a sulphuric acid addition salt of 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula IIA, wherein R_7 , R_{10} and R_{11} are as defined above, into cefixime of formula II.

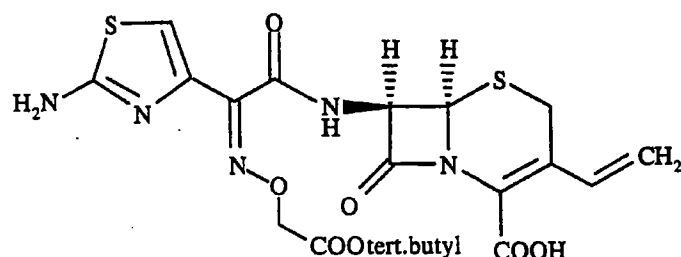
- 25 2. A process according to claim 1, wherein a compound of formula IIIA is 7-amino-3-vinyl-3-cephem-4-carboxylic acid of formula



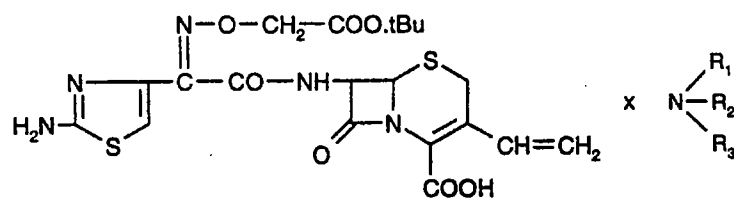
3. A process according to any one of claims 1 to 2, wherein a compound of formula IVA
 5 is 2-(aminothiazol-4-yl)-2-(tert.butoxycarbonyl-methoxyimino)acetic acid S-
 mercaptobenzo-thiazoly-lester of formula



- 10 in form of an N,N-diacetamide solvate.
4. A process according to any one of claims 1 to 3, wherein cefixime of formula II is in
 form of a trihydrate.
- 15 5. 2-(Aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid S-mercapto-
 benzo-thiazoly-lester of formula in form of an N,N-dimethylacetamide solvate.
6. A crystalline salt of a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-
 vinyl-3-cephem-4-carboxylic acid of formula IA, wherein R₇, R₈, R₁₀ and R₁₁ are as
 20 defined in claim 1, with an amine of formula VI, wherein R₁, R₂ and R₃ are as defined
 in claim 1.
7. A salt according to claim 6, wherein a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxy-
 imino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula IA is 7-[2-
 25 (aminothiazol-4-yl)-2-(butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-
 carboxylic acid of formula

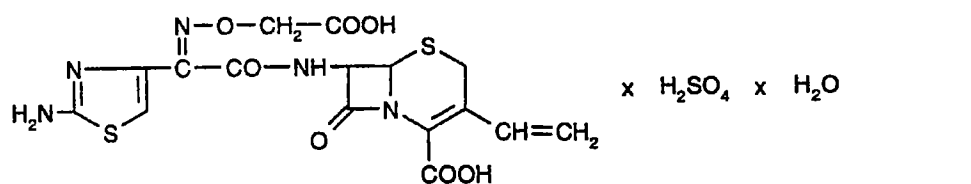


- 5 8. A salt according to anyone of claims 6 to 7 which is a salt of 7-[2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula I with triethylamine, dicyclohexylamine or tert.octylamine.
9. A sulphuric acid addition salt of a compound of formula IIA wherein R_7 , R_{10} and R_{11} are as defined in claim 1.
- 10 10. A salt according to claim 9, wherein a compound of formula IIA is cefixime of formula II.
11. Use of 2-(aminothiazol-4-yl)-2-(tert.butoxycarbonylmethoxyimino)acetic acid S-mercapto-benzo-thiazolylester in form of an N,N-dimethylacetamide solvate; and of a crystalline salt of a 7-[2-(aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula IA, wherein R_7 , R_9 , R_{10} and R_{11} are as defined in claim 1, with an amine of formula VI, wherein R_1 , R_2 and R_3 are as defined in claim 1; and
12. Crystalline salts of 7-[2-(aminothiazol-4-yl)-2-(tert.butoxy-carbonylmethoxyimino)-acetamido]-3-vinyl-3-cephem-4-carboxylic acid of formula



wherein R_1 , R_2 and R_3 either each signify an ethyl group, or R_1 and R_2 are cyclohexyl and R_3 is hydrogen, or R_1 and R_2 are hydrogen and R_3 is the tert.octyl group.

5 13. A crystalline salt of cefixime of formula



INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/00190

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D501/00 C12P17/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0 030 630 A (FUJISAWA PHARMACEUTICAL CO.) 24 June 1981 cited in the application page 132. example 53 -----	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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